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Short Communication

Open letter to IARC Director Christopher P. Wild—Re: IARC Working Group Report 5: *Vitamin D and Cancer*

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Dear Director Wild:

We are writing to urge the IARC to reconsider its position regarding Working Group Report 5: Vitamin D and Cancer.[1] We appreciate the interest of IARC in the role of vitamin D in prevention of cancer. In our view, however, this report is not a satisfactory analysis of the evidence that vitamin D reduces the risk of cancer incidence and mortality rates. The approach and conclusions of the report are not consistent with expert opinion in the field and so the report is not an adequate or fair assessment of the scientific evidence. Major progress has been made in the field of vitamin D and chronic disease but this report fails to report this in a constructive way. We would suggest that you need urgent action to re-assess the field with a more thoroughly researched, better-anchored report which provides the views of established experts in the field. A detailed commentary on numerous errors and omissions in the Report has been published[2] along with a critical editorial commentary concerning flaws in the report.[3]

Some of the serious problems with the Report include:

• It treated the Lappe et al.[4] randomized controlled trial as incidental rather than pivotal in excluding confounding, and ignored the finding that 1,100 IU/day of vitamin D between the ends of the first and fourth years was associated with a 35% reduction in all-cancer incidence. One of the comments in the 2008 IARC Report, that cancer incidence was unusually high in the Lappe et al. placebo group, can easily be shown to be incorrect by calculating the cancer incidence rate from publically available data for that age group and location.[2]

• It treated the Women's Health Initiative (WHI) reports, with their use of a minimal 400 IU dose and extensive noncompliance, as valid aspects of the evidence. However, it was shown in 2004 that such low doses have no preventive value for colorectal cancer.[5] Nonetheless, participants in the WHI study who had serum 25-hydroxyvitamin D [25(OH)D] levels <12 ng/ml at the beginning of the 8 year study had a 253% increased risk of colorectal cancer at the end of the study compared to women who had a 25(OH)D > 23 ng/ml.[6]

• The IARC report makes too little use of the results of distinguished cohort studies such as the Nurses' Health Study and the Male Health Professionals Study cohorts[7] and others.[8,9]

• The report did not make adequate use of the results of modern ecological studies, including studies that used multiple regression analysis to control for confounders. For example, one study of cancer mortality rates in the United States that included indices for numerous cancer risk-modifying factors (summertime solar ultraviolet-B, smoking, alcohol consumption, ethnic background, socioeconomic status, urban/rural residence)[10] was omitted from the IARC report, yet the report claimed that confounding factors were generally 'not included' in ecological studies. Solar UVB irradiance is the primary source of vitamin D for most people. Casual exposure to UVB in summer in the UK increases serum 25-hydroxyvitamin D levels by about 15 ng/mL (~38 nmol/l).[11] It has been established that +15 ng/mL would reduce the risk of colorectal cancer by about 25%[12] and that mortality rates for many types of cancer are inversely correlated with July solar UVB doses in the United States.[10] The use of ecological studies to link solar UVB and vitamin D to cancer risk reduction is reviewed in two recent papers.[13,14]

• There were no clearly stated criteria developed, a priori, upon which the committee was to evaluate the large and rapidly increasing literature on vitamin D and cancer. However, one recent report on risk factors for cancer did do so. In Box 3.8 of *Food, Nutrition, Physical Activity, and the prevention of Cancer: a Global Perspective*[15] the evidence was graded in five categories: 'convincing', 'probable', 'limited—suggestive', 'limited—no conclusion' and 'substantial effect on risk unlikely'.

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For 'convincing' evidence, the following criteria were generally required:-

"Evidence from more than one study type.

Evidence from at least two independent cohort studies.

No substantial unexplained heterogeneity within or between study types in different populations relating to the presence or absence of an association, or direction of effect.

Good quality studies to exclude with confidence the possibility that the observed association results from random or systematic error, including confounding, measurement error and selection bias.

Presence of a plausible biological gradient ('dose response') in the association; such a gradient need not be linear or even in the same direction across the different levels of exposure, so long as this can be explained plausibly.

Strong and plausible experimental evidence, either from human studies or relevant animal models, that typical human exposures can lead to relevant cancer outcomes."

Another widely-accepted set of criteria for causality in a biological system are those published by A. Bradford Hill.[16] Based on the large body of results in the journal literature, it was concluded that vitamin D satisfies these criteria for causality in reducing the risk of cancer incidence and death for many types of cancer.[17]

It is our professional opinion that these criteria are satisfied for hypovitaminosis D and the risk of several types of cancer, especially with the consideration of ecological studies and of the randomized controlled trial by Lappe et al.,[4] well-conducted ecological studies, and internationally respected cohort studies, including the Western Electric Cohort Study,[8] the Johns Hopkins Operation Clue Study[9].

In addition, the study of vitamin D and cancer is very fast moving, and several papers published since November 2008 have added to the evidence for a beneficial role of vitamin D in reducing the risk of cancer incidence or death.[7,18-20] Also, in a review, some of us estimated that if the mean serum 25-hydroxyvitamin D level of Western Europeans were to be raised from about 25 ng/mL to 40 ng/mL, the economic burden of disease there could be reduced by euro187,000 million/year.[21]

Finally, based on the problems we perceive with the IARC 2008 Report[1] as well as the additional errors and omissions detailed by Grant,[2] we urge you give serious consideration to withdrawing the report as being already outdated and at risk of becoming an anachronism in a fast-moving field. Furthermore, we urge you to assemble another committee to produce an updated version, preferably including experts with greater familiarity with the vitamin D/cancer literature.

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